PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Applicant's or agent's file reference see form PCT/ISA/220	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet) **FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2004/037152.	04.11.2004	04.11.2003

International Patent Classification (IPC) or both national classification and IPC
A61K39/395, C12N5/20, A61P33/06, A61P35/02

Applicant
CHIRON CORPORATION

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later. 9-20-05 9-4-05

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
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Form (PCT/ISA/237) (Cover Sheet) (January 2004)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/037152

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

   see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/037152

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 12-31,41-44

because:

☒ the said international application, or the said claims Nos. 12-31,41-44 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/037152

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2-4,6-54
	No:	Claims	1,5
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-54
Industrial applicability (IA)	Yes:	Claims	1-11,32-40,45-54
	No:	Claims	

2. Citations and explanations

see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/US2004/037152

Re Item I
Basis of the report

The sequence listing filed according to the required specifications was filed after the filing date and is therefore not considered as being part of the description (Rule 13ter.1 (f) PCT).

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 12-31, 41-44 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. In some of said methods an in vivo use cannot be excluded. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V
Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents/

D1: WO01/83755
D2: WO02/28904
D3: WO02/88186 (EP1391464)
D4: Ellmark et al., Immunology, 2002;106; pp. 456-463

2. For the assessment of the present claims 12-31,41-44 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

3. Claim 1 is directed to a human antibody, binding to human CD40, without agonist activity and wherein said monoclonal antibody exhibits increased anti-tumor activity relative to an equivalent amount of the monoclonal chimeric anti-CD20 (Rituxan®), wherein the anti-tumor activity is assayed in a staged nude mouse xenograft tumor model using the Daudi human B cell lymphoma cell line. The functional feature relating to the comparison in said precise system, of the anti-tumor activity to the activity of an antibody directed against a different target (CD20) is not a parameter recognized in the art (see GL- 5.36) and renders the claim unclear (Article 6 PCT). The use of said unusual parameter does not allow the comparison of the claimed subject-matter to the antagonist anti-CD40 antibodies of the prior art and therefore the said parameter cannot be taken into consideration when the novelty of claim 1 is determined.

4. D1 discloses human anti-CD40 antibodies, which are a antagonists (page 9, lines 20-25). In view of the previous objection regarding the validity of the unusual parameter, D1 is considered to anticipate the subject-matter of claim 1 (Article 33(2) PCT). D1 discloses also the use of the anti-CD40 antibodies in the treatment of cancer (page 30, lines 1-7) and autoimmune diseases like lupus and rheumatoid arthritis (page 1). Thus the subject-matter of claims 1, 5 is not new (Article 33(2) PCT). The additional feature of independent claim 3 does not confer an inventive step on the antibody because the claimed range of affinity parameters is within the range of affinities expected for a monoclonal antibody. The subject-matter of claims 5-6 does not involve an inventive step because D1 intends to treat cancer in which CD40 expressing B cells are involved (Article 33(3) PCT).

D2 discloses also five human anti-CD40 antibodies, which have an antagonist effect. Said antibodies are disclosed by their sequences (page 3). The proposed use is the treatment of autoimmune diseases, in particular SLE (page 2, line 26); treatment of transplant reactions (page 10, line 16); inhibition of growth of tumor cells (page 10, line 17,) in particular B cell lymphoma (page 13, line 20). D2 shows in figure 1, that several of the human anti-CD40 antibodies are inhibiting the growth of normal B cells, which are stimulated by CD40L (see figure 1). Therefore D2 anticipates the subject-matter of claim 1.

D3 discloses also several human anti-CD40 antibodies, which have an antagonist effect (example 14) .

5. Dependent claim 2 is further limited to the specific monoclonal antibody Chir-12.12, produced by the hybridoma cell line PTA-5543. Said antibody is new (Article 33(2) PCT). Said precise antibody has a very high antitumoral activity as shown in the staged nude mouse xenograft model using Daudi cells. Therefore an inventive step (Article 33(3) PCT) could be acknowledged for said antibody. The present claim 2 is however also directed to a monoclonal antibody, which competes with Chir-12.12 in a competitive binding assay. The data on page 106, last line show that the antibody Chir-5.9, which does not have the high anti-tumoral activity, competes with Chir-12.12 for binding to CD40. As the antibody Chir-5.9 is only a further human antibody which has an antagonist activity on CD40 and which does not have any other surprising features, an inventive step can not be acknowledged for the antibody Chir-5.9 and as a consequence also not for section g) of claim 2 (Article 33(3) PCT) and for claims 7-9, 10, 11. Claim 45 is directed to a pharmaceutical composition comprising monoclonal antibody Chir-5.9. As the human monoclonal antibodies of D1 and D2 are intended for medical use, the subject-matter of independent claim 45 also lacks an inventive step. Dependent claims 46-54 refer to features commonly present in pharmaceutical compositions and thus do not confer an inventive step on the composition (Article 33(3) PCT).

Independent claims 12,15,18,21,25,29,41 are directed to methods for inhibiting growth of normal or tumor B cells expressing CD40, for treating autoimmune diseases and for inhibiting the CD40-mediated pathway. All these methods use also antibody Chir-5.9, which is novel but does not involve an inventive step (see above). As both D1 and D2 have disclosed the use of human antibodies, which are antagonists of anti-CD40 and which inhibit the growth of normal and malignant B cells (treatment of B cell cancer), which are useful in the treatment of autoimmune diseases and which as antagonists, inherently inhibit the CD40-CD40L mediated pathway, the subject-matter of independent claims 12,15,18,21,25,29,41 does not involve an inventive step (Article 33(3) PCT). The additional features of the respective dependent claims 13,14,16,17,19,20,23,24, 26-28,30,31,42-44 do not confer an inventive step on the methods.

6. Claim 32 is directed to a method for identifying antibodies having antagonist activities by performing a competitive binding assay against Chir-5.9 or Chir-12.12. Said method is novel, but as Chir-5.9 (see section 5) does not involve an inventive step and as the use of competitive binding assays for detecting antibodies having similar properties as the competing partner is a standard procedure, the subject-matter of claim 32 does not involve an inventive step.

Claim 33 is directed to an antagonist antibody, which specifically binds to domain 2 of CD40. Data of the present application show that Chir-5.9 binds also to domain 2 of CD40 and Chir-5.9 (only a further antagonist) does not show any surprising feature. D4 (figures 1 and 3) shows that a single chain antibody F33, which also has an antagonist activity binds to domain 2 and states that the region of CD40 involved in CD40-CD40L binding is located in the D2 and D3 domain. Therefore the fact per se that the antibody binds to the known domain 2 of CD40 does not involve an inventive step (Article 33(3) PCT). The subject-matter of claims 34-38, 40 all dependent on claim 33, does not involve in inventive step because it comprises the non-inventive antibody Chir-5.9 (see section 5 above). In the case of claim 40, Chir-5.9 was shown to compete with Chir12.12 and falls within the scope of section e).

The characterisation of the respective epitopes of CD40, to which the antibodies Chir-5.9 and Chir-12.12 are binding (tables 17 and 18) show that the epitope to which the non-inventive antibody Chir-5.9 (see above) binds, comprises positions 82-87. Therefore the subject-matter of claim 39 does not involve an inventive step (Article 33(3) PCT).

Further Remarks:

7. The claims are not clear (Article 6 PCT) because the internal denomination CHIR-12.12 is not a generally recognised name.